The novel 5-HT_{1A} receptor antagonist, SDZ 216-525, decreases 5-HT release in rat hippocampus *in vivo*

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1 Recent evidence suggests that the novel compound SDZ 216-525 is a selective and possibly silent 5-HT_{1A} receptor antagonist. Here we have examined the action of SDZ 216-525 on central 5-HT_{1A} autoreceptor function. The experiments involved measurement of drug effects on extracellular 5-HT in the ventral hippocampus of the chloral hydrate anaesthetized rat by use of microdialysis.

2 Acute injection of SDZ 216-525 (0.1, 0.3, 1.0 and 3 mg kg⁻¹, s.c.) caused a dose-related decrease in 5-HT output with an estimated ED₅₀ of at least 0.3 mg kg⁻¹. This ED₅₀ value is 20–30 times greater than ED₅₀ values previously obtained for 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) and NAN-190. In comparison, SDZ 216-525 is reported to have slightly higher affinity for the 5-HT_{1A} site than 8-OH-DPAT and NAN-190.

3 The inhibitory effect of SDZ 216-525 (1 mg kg⁻¹, s.c.) on 5-HT was blocked by the 5-HT₁/β-adrenoceptor antagonist, (–)-pindolol (8 mg kg⁻¹, s.c.) but not by a combination of the β₁- and β₂-selective adrenoceptor antagonists metoprolol and ICI 118,551 (4 mg kg⁻¹, each).

4 Although in several experimental models SDZ 216-525 has high affinity, selectivity and lacks intrinsic activity at the 5-HT_{1A} receptor, our experiments show that the drug decreases extracellular 5-HT in ventral hippocampus of the chloral hydrate anaesthetized rat via a pindolol-sensitive mechanism. We conclude that either SDZ 216-525 promotes (with low potency *in vivo*) 5-HT_{1A} receptor/G-protein interactions, or that the 5-HT_{1A} autoreceptor is a 5-HT_{1A} receptor subtype different from the postsynaptic 5-HT_{1A} receptor.

Keywords: SDZ 216-525; 5-HT_{1A} receptor; microdialysis; 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT); NAN-190

Introduction

Currently studies on the pharmacology of the 5-HT_{1A} receptor are hampered by the lack of suitable drug tools. Thus, whilst there are available a number of high affinity 5-HT_{1A} receptor ligands, most either lack selectivity and/or display mixed agonist/antagonist properties.

Recently, the pharmacological properties of the 5-HT_{1A} receptor ligand, SDZ 216-525, (methyl-4-[4-(1,1,3-trioxo-2H-1,2-benzisothiazol-2-yl) butyl]-1-piperazinyl) 1H-indole-2-carboxylate; Compound 24, Seiler *et al.*, 1992) were described (Hoyer *et al.*, 1992; Boddeke *et al.*, 1992; Schoeffter *et al.*, 1993). This compound displays high affinity and selectivity for brain 5-HT_{1A} binding sites versus other binding sites for 5-hydroxytryptamine (5-HT) (5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT₂, 5-HT₃) and other neurotransmitters (α₁, α₂, β₁, β₂ and D₂). In biochemical studies using receptor-linked effector systems, SDZ 216-525 potently antagonizes the effects of the selective agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) on 5-HT_{1A} receptors (pK_B = 10) but displays no intrinsic activity. In comparison, SDZ 216-525 has little affinity or activity in biochemical models of 5-HT_{1B}, 5-HT_{1C} or 5-HT_{1D} receptor function. Evidence from *in vivo* experiments also suggests that SDZ 216-525 is a potent and possibly silent 5-HT_{1A} receptor antagonist. Thus, in the rat the drug does not induce forepaw treading, flat-body posture and hypothermia but inhibits these responses when induced by 8-OH-DPAT (Hoyer *et al.*, 1992; Schoeffter *et al.*, 1993).

A number of high affinity 5-HT_{1A} receptor ligands, including NAN-190 and BMY 7378, which display low intrinsic activity at the 5-HT_{1A} receptor in many models of 5-HT_{1A} receptor function, seemingly have agonist activity at the somatodendritic 5-HT_{1A} autoreceptor. This activity is apparent in both electrophysiological studies which show that NAN-190 and BMY 7378 inhibit the firing of raphe 5-HT

neurones (VanderMaelen *et al.*, 1986; Greuel & Glaser, 1992; Hodgkiss *et al.*, 1992) and neurochemical studies which show that these drugs decrease 5-HT release *in vivo* (Sharp *et al.*, 1990; Sharp & Hjorth, 1990; Hjorth & Sharp, 1990). Here we have tested the effect of SDZ 216-525 on 5-HT_{1A} autoreceptor function using the latter approach.

Methods

In vivo measurement of 5-HT release using microdialysis

The microdialysis procedure used is described in detail elsewhere (Sharp *et al.*, 1989). In brief, male Sprague Dawley rats (260–360 g, Harlan-Olac, Bicester, U.K.) were anaesthetized with chloral hydrate and a microdialysis probe (short-loop type, Cordis Dow cellulose membrane) was stereotactically implanted into the ventral hippocampus (stereotaxic co-ordinates: anterior-posterior – 4.0 mm, lateral – 4.6 mm, dorsal-ventral – 8.5 mm, relative to bregma and dura surface with a head-flat position). The microdialysis probe was perfused continuously (1 μl min⁻¹) with artificial CSF containing 1 μM citalopram, a selective 5-HT reuptake inhibitor. Perfusates were collected every 20 min and analysed immediately for 5-HT by high performance liquid chromatography with electrochemical detection.

Experimental protocol

After probe implantation, there followed a control period of about 3 h to allow the level of 5-HT in the perfusates to stabilize. Drugs were then injected subcutaneously over the next 30 min and 5-HT measurements were continued for a further 2 h.

SDZ 216-525 was tested in two groups of experiments; (i)

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SDZ 216-525 was administered alone to naive rats, and (ii) SDZ 216-525 was administered to rats pretreated 30 min previously with either the 5-HT₁/β-adrenoceptor antagonist (–)-pindolol or the β-adrenoceptor antagonists, metoprolol (β₁) and ICI 118,551 (β₂), in combination.

Drugs

SDZ 216-525 (methyl 4-[4-(1,1,3-trioxo-2H-1,2-benziothiazol-2-yl)butyl]-1-piperazinyl]1H-indole-2-carboxylate, synthesized at SANDOZ Pharma, Basel, Switzerland) was dissolved in malonic acid (5 mg compound mixed with 5 mg malonic acid in 1 ml water). Metoprolol tartrate (Hassle, Mölndal, Sweden) and ICI 118,551 ((±)-erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylamino-butan-2-ol HCl; ICI, Macclesfield, U.K.) were dissolved in saline. (–)-Pindolol (SANDOZ Pharma, Basel, Switzerland) was dissolved in a few drops of glacial acetic acid and made up to volume in 5% (w/v) glucose solution. Drugs were injected subcutaneously in a volume of 1 ml kg⁻¹.

Data presentation and analysis

5-HT in the perfusates over time is expressed as a percentage of the absolute amount of 5-HT in the sample obtained immediately before drug administration. This method of presentation allows direct comparison of the present data with those of our earlier studies. Using percentage data, areas under the curve for the 0–120 min period postdrug were calculated and used to construct a dose-response curve. ED₅₀ values were estimated graphically.

Treatment effects were analysed statistically (using raw data) either by within group comparisons (pre versus post-treatment) using 1-way ANOVA with repeated measures (followed by Dunnett's test) or by between group comparisons using 2-way ANOVA with repeated measures. Probability values of 0.05 or less were considered to be statistically significant.

Results

Effect of administration of SDZ 216-525 on 5-HT release in hippocampus of naive rats

In chloral hydrate anaesthetized, treatment-naive rats injection of SDZ 216-525 induced a clear-cut and dose-related (0.1, 0.3, 1 and 3 mg kg⁻¹, s.c.) decrease in 5-HT levels in hippocampal microdialysates (Figure 1). 5-HT levels decreased to about 50% of pre-drug values by 120 min following injection of 1 mg kg⁻¹ SDZ 216-525. The highest dose tested (3 mg kg⁻¹, s.c.) also reduced 5-HT levels to about 50% of pre-drug values but within 60 min of injection. A higher dose was not tested due to poor drug solubility at high concentrations.

In comparison to SDZ 216-525, injection of malonic acid vehicle did not alter 5-HT output over the 2 h post drug period compared to pre-injection control values (Figure 1).

Statistical analysis (1 way ANOVA followed by Dunnett's test) of the data revealed significant effects of SDZ 216-525 at all doses tested but no effect of vehicle injection when compared to pretreatment values.

Figure 2 compares the dose-response curve for SDZ 216-525 with curves previously published for 8-OH-DPAT and NAN-190. The latter data were obtained in experiments carried out under identical conditions to those described in the present paper. From these curves it is estimated that the ED₅₀ for SDZ 216-525 is at least 0.3 mg kg⁻¹, s.c. which is 20–30 times greater than corresponding ED₅₀ values for 8-OH-DPAT (0.015 mg kg⁻¹, s.c.) and NAN-190 (0.009 mg kg⁻¹, s.c.). Note that the maximum suppression of 5-HT release detected following both NAN-190 and SDZ 216-525 was less than that following 8-OH-DPAT (Figure 2).

Figure 1 Effect of different doses of SDZ 216-525 and malonic acid vehicle on 5-hydroxytryptamine (5-HT) in microdialysates from ventral hippocampus of the chloral hydrate anaesthetized rat. Treatment groups are identified as follows: malonic acid vehicle (○, *n* = 6); 0.1 mg kg⁻¹ (●, *n* = 4); 0.3 mg kg⁻¹ (□, *n* = 6); 1 mg kg⁻¹ (■, *n* = 7); 3 mg kg⁻¹ (△, *n* = 3). 5-HT in the microdialysates is expressed as a % (mean ± s.e.mean) of the absolute amount of 5-HT in the sample collected immediately before drug injection (*t* = 0). Absolute amounts of 5-HT (pmol/sample, mean ± s.e.mean) at *t* = 0 were as follows: controls: 0.061 ± 0.006; 0.1 mg kg⁻¹: 0.056 ± 0.004; 0.3 mg kg⁻¹: 0.069 ± 0.010; 1 mg kg⁻¹: 0.060 ± 0.006; 3 mg kg⁻¹: 0.066 ± 0.004. See results for details of statistical analysis.

Figure 2 Log-dose response curves for the inhibitory effect of SDZ 216-525 (□), 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) (○) and NAN-190 (●) on 5-hydroxytryptamine (5-HT) output in ventral hippocampus of the chloral hydrate anaesthetized rat. The values for 5-HT are calculated from the areas under the curve (AUC) for the 0–120 min period post drug injection and are expressed as a % of control (the dotted line at 100% represents no change). The time course data for SDZ 216-525 are shown in Figure 1. The data for 8-OH-DPAT and NAN-190 are taken in part from Sharp *et al.* (1989) and Hjorth & Sharp (1990). Each point is a mean ± s.e.mean value.

Effect of pretreatment with (–)-pindolol, metoprolol and ICI 118,551 on the 5-HT response to SDZ 216-525

The 5-HT response to 1 mg kg^{-1} , s.c., SDZ 216-525 was blocked in rats pretreated with 8 mg kg^{-1} , s.c. of the 5-HT_{1A} / β -antagonist (–)-pindolol (Figure 3). In contrast, the 5-HT response to SDZ 216-525 persisted in rats pretreated with a combination of 4 mg kg^{-1} , s.c. of each of the β -blockers metoprolol and ICI 118,551 (Figure 3). Neither (–)-pindolol nor metoprolol and ICI 118,551 altered basal 5-HT output when injected alone in these experiments (Hjorth & Sharp, 1993).

Statistical analysis of the data using 1-way ANOVA (followed by Dunnett's test) revealed significant changes in 5-HT ($P < 0.05$) following 1 mg kg^{-1} SDZ 216-525 alone or in combination with metoprolol and ICI 118,551 but no significant changes ($P > 0.05$) after 1 mg kg^{-1} SDZ 216-525 in combination with (–)-pindolol. Statistical analysis of the data by 2-way ANOVA revealed a significant interaction between the SDZ 216-525 alone versus SDZ 216-525 plus (–)-pindolol ($F = 4.172$, d.f. 8, 88; $P < 0.001$) but no interaction between SDZ 216-525 alone versus SDZ 216-525 plus β -blockers ($F = 0.702$, d.f. 8, 72; $P = 0.689$).

Discussion

Here we show that the novel and putative silent 5-HT_{1A} receptor antagonist, SDZ 216-525, induces a clear-cut and dose-related decrease in extracellular 5-HT in the ventral hippocampus of anaesthetized rats. This response is blocked by pretreatment with the $5\text{-HT}_1/\beta$ -adrenoceptor-antagonist (–)-pindolol but not the control β -adrenoceptor antagonists, metoprolol and ICI 118,551. This implicates the involvement of receptors of the 5-HT_1 subtype rather than other receptors of 5-HT or indeed receptors of other neurotransmitters. Given the high affinity and selectivity of SDZ 216-525 for the 5-HT_{1A} binding sites versus other binding sites for 5-HT (5-HT_{1B} , 5-HT_{1C} , 5-HT_{1D} , 5-HT_2 , 5-HT_3) and other neurotransmitters

Figure 3 Effect of pretreatment with the $5\text{-HT}_1/\beta$ -adrenoceptor antagonist (–)-pindolol (8 mg kg^{-1} , s.c.) and a combination of the β_1 - and β_2 -selective adrenoceptor antagonists, metoprolol and ICI 118,551 (each at 4 mg kg^{-1} , s.c.) on the inhibitory effect of SDZ 216-525 (1 mg kg^{-1} , s.c.) on 5-hydroxytryptamine (5-HT) output in the ventral hippocampus. Treatment groups are identified as follows: controls (○, $n = 6$); SDZ 216-525 alone (●, $n = 7$); SDZ 216-525 plus (–)-pindolol (□, $n = 6$); SDZ 216-525 plus metoprolol and ICI 118,551 (■, $n = 4$). Absolute amounts of 5-HT (pmol/sample, mean $\pm$ s.e.mean) at $t = 0$ were as follows: controls: 0.061 ± 0.006 ; SDZ 216-525: 0.060 ± 0.006 ; SDZ 216-525 plus (–)-pindolol: 0.048 ± 0.003 ; SDZ 216-525 plus metoprolol and ICI 118,551: 0.048 ± 0.005 . See results for details of statistical analysis.

(α_1 , α_2 , β_1 , β_2 and D_2 ; Hoyer *et al.*, 1992; Schoeffter *et al.*, 1993), a strong candidate for the mechanism underlying the inhibition of 5-HT release by SDZ 216-525 is activation of 5-HT_{1A} autoreceptors, probably those located on the soma and dendrites of 5-HT neurones in the midbrain raphe.

In conflict with the present findings, biochemical studies to date indicate that SDZ 216-525 lacks intrinsic activity at the 5-HT_{1A} receptor. Thus, the drug does not inhibit forskolin-stimulated adenylate cyclase in calf hippocampal membranes but antagonizes potentially the inhibition induced by 8-OH-DPAT (Hoyer *et al.*, 1992; Schoeffter *et al.*, 1993). Furthermore, in another biochemical model of 5-HT_{1A} receptor function, 5-HT_{1A} -mediated calcium mobilization in Hela cells, SDZ 216-525 displays the property of a potent and silent 5-HT_{1A} receptor antagonist even under conditions of high receptor reserve which favours the expression of intrinsic activity (Boddeke *et al.*, 1992). Findings from studies using *in vivo* models of 5-HT_{1A} receptor function also support the idea that SDZ 216-525 is a 5-HT_{1A} receptor antagonist lacking intrinsic activity. Specifically, in the rat SDZ 216-525 ($0.03\text{--}1 \text{ mg kg}^{-1}$, s.c.) blocks 8-OH-DPAT-induced forepaw treading, flat-body posture and hypothermia without inducing these effects itself (Hoyer *et al.*, 1992; Schoeffter *et al.*, 1993).

Previously we have reported that a number of 5-HT_{1A} receptor ligands with apparently low intrinsic activity at the 5-HT_{1A} receptor, including NAN-190 and BMY 7378, also decrease 5-HT release in hippocampus via a pindolol-sensitive mechanism (Sharp *et al.*, 1990; Hjorth & Sharp, 1990). Furthermore, both NAN-190 and BMY 7378 inhibit the firing of 5-HT neurones when applied locally to the raphe (VanderMaelen *et al.*, 1986; Hodgkiss *et al.*, 1992), the latter effect being antagonized by high concentrations of the $5\text{-HT}_1/\beta$ -adrenoceptor-antagonist, (–)-propranolol (Greuel & Glaser, 1992). These findings have led to the idea that NAN-190 and BMY 7378 are weak partial 5-HT_{1A} receptor agonists and not silent 5-HT_{1A} receptor antagonists.

It seems reasonable to assume that SDZ 216-525 is also a partial 5-HT_{1A} agonist on the basis of the present findings that first, SDZ 216-525 decreased 5-HT release when injected alone but with an efficacy likely to be less than that of 8-OH-DPAT (cf. Figure 2) and secondly, the inhibitory effect of SDZ 216-525 on 5-HT was blocked by (–)-pindolol. The present data do not exclude the possibility that blockade of α_1 -adrenoceptors has a part to play in the 5-HT response to SDZ 216-525, a mechanism which may contribute to the decrease in 5-HT release induced by NAN-190 (Hjorth & Sharp, 1990; Claustre *et al.*, 1991). However, it should be pointed out that data from binding studies show that the affinity of SDZ 216-525 for α_1 -adrenoceptors is about 70 times lower than that for 5-HT_{1A} receptors (Schoeffter *et al.*, 1993).

It remains to be determined why 5-HT_{1A} ligands with low intrinsic activity at the 5-HT_{1A} receptor, apparently express agonist activity at the 5-HT_{1A} autoreceptor. Plausible explanations include high 5-HT_{1A} receptor reserve in the raphe (Meller *et al.*, 1990), high efficiency coupling between this receptor and its effector mechanisms and even differences in 5-HT_{1A} receptor subtype in the raphe compared to other brain regions (Radja *et al.*, 1992).

The results of biochemical studies showing that SDZ 216-525 does not display 5-HT_{1A} receptor agonist activity under conditions where receptor reserve is high (Boddeke *et al.*, 1992), suggests that the coupling between the 5-HT_{1A} autoreceptor and its effector mechanisms may be a more important factor. If 5-HT_{1A} autoreceptors are extremely well coupled to their effector system as suggested (Meller *et al.*, 1990; Sharp *et al.*, 1990), compounds with very low or no intrinsic activity at postsynaptic 5-HT_{1A} receptors may display agonism at autoreceptors. However, some of these compounds act as agonists at concentrations significantly higher than those expected from radioligand binding studies (also see below).

Support for the view that there are 5-HT_{1A} receptor subtypes comes from the present observation that the potency of SDZ 216-525 at inhibiting 5-HT release ($ED_{50} = 0.3 \text{ mg kg}^{-1}$, s.c.) is some 20–30 times less than that of 8-OH-DPAT (0.015 mg kg^{-1} , s.c.) and NAN-190 (0.009 mg kg^{-1} , s.c.) whereas the affinity of SDZ 216-525 for the 5-HT_{1A} binding site ($pK_D = 9.2$) is slightly greater than that of 8-OH-DPAT (8.7) and NAN-190 (8.9). Clearly, differences between potency *in vivo* and binding affinity *in vitro* could be explained by poor entry of SDZ 216-525 into the brain; the action of an active metabolite cannot be excluded. It ought to be added, however, that it was reported very recently that SDZ 216-525 (1 mg kg^{-1} , s.c.) decreased hippocampal 5-HT release (as measured by microdialysis) but that this effect was not blocked by the putative silent 5-HT_{1A} receptor anta-

gonist, ($\pm$)-WAY 100135 (Gurling *et al.*, 1993). The interesting possibility that SDZ 216-525 is differentially sensitive to (–)-pindolol and ($\pm$)-WAY 100135 deserves further investigation.

In conclusion, the present study shows that the novel compound SDZ 216-525 decreases 5-HT release in rat hippocampus *in vivo* via a pindolol-sensitive mechanism. It is possible that this compound is a weak partial 5-HT_{1A} receptor agonist rather than a silent 5-HT_{1A} receptor antagonist as recent biochemical studies suggest. This matter, however, warrants further study given the continuing speculation concerning 5-HT_{1A} receptor subtypes.

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